

## CME RECOGNITION

This SKIN & ALLERGY NEWS supplement is recognized by the American Academy of Dermatology (AAD) for 1 hour of AAD Category 1 CME credit and may be used toward the American Academy of Dermatology's Continuing Medical Education Award.

This program was developed in accordance with the Accreditation Council for Continuing Medical Education guidelines.

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**Estimated time to complete this educational activity:** 1 hour

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## TARGET AUDIENCE

This activity has been developed for dermatologists and other health care professionals involved in the diagnosis and treatment of skin conditions for which immune response modifier (IRM) therapy may be considered.

## EDUCATIONAL NEEDS

Actinic keratoses (AKs) and common warts are lesions that are difficult to eliminate. Traditional therapies—surgical and topical chemical modalities—can be effective, but none of these has been shown to produce remission in all patients.

IRM therapy is a relatively recent approach to eliminating AKs and lesions caused by human papillomavirus (HPV). In both cases, topical imiquimod—the first agent in the class of IRMs—causes an upregulation of several mechanisms that control local immune system function.

To date, imiquimod has been approved by the US Food and Drug Administration for the treatment of anogenital warts, superficial basal cell carcinoma, and AKs of the face and balding scalp. In the cases presented here, imiquimod was used investigatively as a potential prophylactic treatment for AKs in patients with photodamaged facial skin who, by definition, are at increased risk for AKs and, possibly, subsequent squamous cell carcinoma. In the cases of common warts, imiquimod was used based on the efficacy of this agent in treating anogenital warts, also caused by infection with HPV.

The results of well-controlled clinical trials form the foundation of an evidence-based approach to medical treatment. In treating individual patients, however, clinicians also receive valuable knowledge from their own experience and that of their colleagues. Using case studies as a basis, this supplement offers the clinical experiences of experts who have used imiquimod in a variety of skin diseases.

## LEARNING OBJECTIVES

By reading and studying this supplement, participants should be able to:

- Briefly summarize what is currently understood about the antiviral and antitumor properties and mechanism of action of imiquimod.
- Describe the experience of a clinician who treated a patient enrolled in a study involving the use of imiquimod to prevent the emergence of subclinical AKs.
- Discuss the experience of a clinician who used imiquimod to treat two patients with recalcitrant warts—one with a plantar wart and one with periungual warts of the fingers.

## FACULTY AND UNAPPROVED USE DISCLOSURES

Faculty/authors must disclose any significant financial interest or relationship with proprietary entities that may have a direct relationship to the subject matter. The faculty must also disclose any discussion of investigational or unlabeled uses of products.

**Dr Effron** is on the Speaker's Bureau and the Aldara Advisory Panel at 3M Pharmaceuticals. She refers to a discussion elsewhere in this supplement of the unlabeled use of imiquimod for the prevention of AKs and for the treatment of plantar and periungual warts. **Dr Kligman** has no financial disclosures. He discusses the unlabeled use of imiquimod for the prevention of AKs. **Dr Skinner** is on the Speaker's Bureau and the Aldara Advisory Panel at 3M Pharmaceuticals. He discusses the unlabeled use of imiquimod for the treatment of plantar and periungual warts.



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# DERMATOLOGISTS' CASE FILES

## Immune Response Modifier Therapy Used With Good Results in Recalcitrant Warts and Photoaging

Cheryl L. Effron, MD

### Introduction



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In this, the second of four issues of *Dermatologists' Case Files*, our faculty focuses on two types of warts and the unexpected results of a clinical study of actinic keratosis (AK).

Robert B. Skinner, Jr, MD, addresses two cases from his practice, one a middle-aged airline pilot with a large plantar wart and the other a 12-year-old boy with periungual warts. In both cases, the human papillomavirus (HPV) infection was refractory to treatment with standard modalities. Also in both cases, the patients' normal daily activities were adversely affected by their HPV infection. In addition, the patient with periungual warts on his hands was embarrassed by their appearance, which, for a child his age, is an experience that can be as uncomfortable as the lesions themselves. Because trials with traditional treatment methods had failed repeatedly in both patients, Dr Skinner turned to the strategy of immune response modifier treatment, with good results.

Albert M. Kligman, MD, PhD, discusses a patient who was involved in a small clinical

trial exploring the potential use of immune response modifier therapy to prevent sun-related damage and subsequent development of AKs.

The importance of treating AKs has come to light in recent years with the increasing understanding of the association between these lesions and invasive squamous cell carcinoma (SCC). AK is a US Food and Drug Administration-approved indication for imiquimod, and photodamage is a recognized cause of both AKs and SCC. It is reasonable to explore the possibility that the same local immune response that eliminates AKs—including subclinical, nonvisible lesions—might be a valuable prophylactic strategy.

During Dr Kligman's study of a small group of patients with photodamaged facial skin investigating imiquimod as a preventive treatment for AKs, he observed an unintended benefit of such treatment: improvement in the skin's cosmetic appearance as a result of a decrease in the signs of early photodamage.

All three patients illustrate a principle that dermatologists face every day in clinical practice: many of our patients do not seek our help because their lives are threatened by a disease but because the quality of their lives is affected. When standard approaches fail, an innovative strategy may be helpful for the patient and satisfying for the clinician. ■

Please go to [www.managingactinickeratoses.com](http://www.managingactinickeratoses.com)  
for more information on the treatment of actinic keratoses.

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## Photodamage in a 46-Year-Old Woman

Albert M. Kligman, MD, PhD

The patient is a 46-year-old white woman, phototype III, who is in good health and taking no medications, with a history of unprotected sun exposure during summer vacations. She shows the typical signs of moderate photodamage—periorbital wrinkles, accentuated fine lines, mottled pigmentation, rough-dry scaling, and poor texture.

She agreed to participate in a small study of the benefit of imiquimod in preventing actinic keratoses (AKs) in sun-damaged skin. She was one of 10 women between 45 and 55 years of age who had similar signs of sun-induced skin damage, yet no visible AKs.

The presence of photodamage characteristic of subclinical AKs was demonstrated histologically prior to the initiation of treatment. The purpose of the study—based on the concept of field cancerization and field therapy—was to determine whether imiquimod use would prevent the emergence of clinically apparent AKs.

She was treated with imiquimod 5 days a week for 4 weeks (the regimen approved for the treatment of AKs by the US Food and Drug Administration [FDA] is thrice-weekly applications for 16 weeks). After 4 weeks, the patient's fine wrinkles were no longer visible (Figure). In addition, her clogged pores had resolved and surface irregularities and poor texture were substantially reduced, and her skin looked and felt smoother to the touch.

The topical retinoid tretinoin has been approved by the

FDA for the cosmetic treatment of the signs of photodamage mentioned above. In addition, procedures such as microdermabrasion, chemical peels, and laser treatments are widely used to reduce such visible signs of aging. In addition to imiquimod, FDA-approved topical treatments for AKs are diclofenac, 5-fluorouracil, and photodynamic therapy.

### Discussion

The benefits of imiquimod in the treatment of AKs have been well documented,<sup>1</sup> and the effects of this agent on both visible and subclinical lesions (as demonstrated histologically in the reduction of keratinocytic atypia in the epidermis) have been extensively reported.

In our study, pretreatment histochemical examination demonstrated epidermal atrophy,



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keratinocytic atypia, diffuse dysplasia with poor differentiation, lack of polarity, hyperchromatic nuclei, and marked differences in staining, sizes, and shapes of keratinocytes. These features are traditionally called pre-malignant changes and are characteristic of the photodamaged epidermis in which AKs develop.

The posttreatment specimens showed complete correction of atrophy and atypia, with a greatly enhanced granular layer, and restoration of differentiation and polarity.

### Conclusion

This patient entered a study designed to test the possible benefits of using imiquimod to prevent the emergence of clinically apparent AKs. Her response to topical applications of

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Figure. Right Periorbital Area, Female Patient



Digital photographs taken before (left) and after (right) treatment with imiquimod demonstrate the resolution of many of the fine periorbital wrinkles that are characteristic early signs of photodamage.

## Man With a Large Plantar Wart

Robert B. Skinner, Jr, MD

A 52-year-old airline pilot presented with a painful, verrucous lesion on the plantar aspect of his foot that had first appeared more than 1 year earlier. During this time, the lesion had increased in size until, at the time of presentation, it involved approximately 33% of the sole of the patient's foot (**Figure**). The diagnosis of a plantar wart was readily apparent from the patient's history and the clinical appearance of the wart.

Treatment with liquid nitrogen almost every 3 weeks for 6 months resulted in no improvement; indeed, the lesion continued to increase in size. Because imiquimod has demonstrated local immunity-enhancing properties and has been used successfully for more than a decade to treat genital warts (also caused by human papillomaviruses [HPVs]), it seemed reasonable to try using this agent as an adjunct to continued applications of liquid nitrogen.

The patient was instructed to apply imiquimod nightly under occlusion with duct tape. In the morning, he was to remove the tape and wash the treated area, then apply 40% urea gel. Liquid nitrogen therapy was used on a thrice-weekly schedule.

For 3 months, no clinical changes were noted. After this time, however, rapid resolution of the wart ensued, and after a total of 6 months of the combination therapy, the lesion had completely cleared.

### Discussion

The traditional treatments for common warts include both

physician-applied modalities—cryosurgery (with or without electrodesiccation), carbon dioxide laser, intralesional injections of bleomycin—and patient-applied therapies—salicylic acid or lactic acid, alone or under occlusion. (Cantharidin is another traditional treatment, but is not currently in widespread use in the United States.)

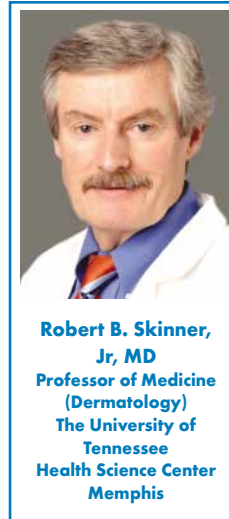
Plantar and periungual warts are categorized as common warts and are caused by infection with nononcogenic types of HPV, typically, types 1, 2, 4, 27, and 29. Anogenital warts are most commonly caused by HPV types 6, 11, 16, 18, and 33. The immune response modifier imiquimod is approved by the US Food and Drug Administration for the treatment of anogenital warts, and although the HPV types that cause anogenital warts differ from the types that are associated with common warts, all HPV types seem to share the same route of infection and the mechanism of action of imiquimod in clearing HPV has not been shown to be type-specific.

The exact mechanism of action of imiquimod's antitumor and antiviral effects continues to be explored and the results of these investigations have revealed much about the immune system, both innate and acquired.

In the case of HPV, specifically, the human cellular-mediated immune response fails to reach HPV within infected keratinocytes. From its protected milieu, HPV produces peptides that cause keratinocyte prolifer-

ation and, thus, warts. Imiquimod induces an immune response characterized by the production of interferon-alpha, a cytokine that inhibits the reproduction of HPV in cells already infected, protects adjacent cells from becoming infected, and causes upregulation of local antiviral activity, including that of natural killer cells.<sup>1</sup>

Promising results were achieved in a study of imiquimod monotherapy for common warts.<sup>2</sup> Sparling and colleagues<sup>3</sup> achieved improved results with imiquimod used under occlusion and in combination with cryotherapy. The results of these small studies—as well as the anecdotal experiences of many



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dermatologists—suggest that controlled clinical trials of imiquimod in common warts are warranted. Such studies might include the impact on imiquimod efficacy of various combinations of imiquimod with traditional therapies, as well as testing the suggestion that abrading these hyperkeratotic lesions prior to treatment might result in better, faster penetration of this agent.

### Conclusion

The patient recently came to my office again for an unrelated problem. He reported that the wart had not

*Continued on page 4*

**Figure. Large Plantar Wart**



Because of its location and size, this patient's plantar wart (left) was painful and interfered with his daily functioning. After 3 months of adjunctive treatment with imiquimod, the lesion was markedly improved (right). Complete clearance was noted by 6 months on the combination regimen with liquid nitrogen, 40% urea gel, and imiquimod under occlusion.

## Recalcitrant Periungual Warts in a 12-Year-Old Boy

Robert B. Skinner, Jr, MD

The patient is a 12-year-old boy with extensive periungual warts that involved six fingers (Figure). He had been treated by his pediatrician for approximately 3 months with liquid nitrogen, with no improvement. Following this, an over-the-counter salicylic acid preparation was tried for about 2 months, also with no effect. A subsequent treatment attempt involved a regimen of liquid ni-

trogen plus salicylic acid, a strategy that also was not successful.

When he was seen in our office, the patient's mother reported that his condition had not improved at all and that the youngster was experiencing intense embarrassment at school and social activities.

Because the patient's fingers had become exquisitely tender following liquid nitrogen therapy, subsequent liquid nitrogen

treatments were preceded by a topical anesthetic that the patient was instructed to apply at home before his office visit. In addition, the treatment schedule was adjusted to every 4 weeks to provide the patient with some additional recovery time between liquid nitrogen applications. In an attempt to enhance the effectiveness of the liquid nitrogen therapy, I instructed the patient to apply imiquimod in the evening under occlusion with duct tape; in the morning, he was to remove the tape and wash his hands, then apply 40% urea gel.

For almost 3 months, no change was evident in the patient's condition. After this time, however, resolution of the warts began and progressed gradually. At 5 months, the warts had completely resolved.

### Conclusion

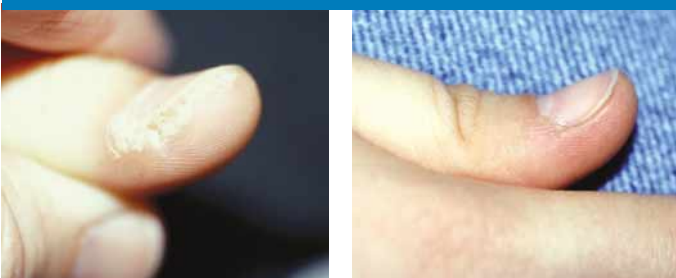
As with the patient with the large plantar wart (dis-

cussed on page 3), the addition of imiquimod to the traditional treatment regimen of liquid nitrogen therapy appeared to enhance the efficacy of a previously unsuccessful treatment strategy. The time to the beginning of the resolution of the warts—both in this case and in the case of the airline pilot with the large plantar wart—was 3 months, which is not surprising when one considers that imiquimod's mechanism of action is upregulation of the local immune system.

The successful result of this combination therapy was both the clinical resolution of the signs and symptoms of this patient's human papillomavirus infection and the improvement in his physical comfort and quality of life. ■

*(Further discussion of the rationale for the use of imiquimod in common warts is provided in the case of a patient with a large plantar wart, page 3.)*

Figure. Severe Periungual Warts



This young man had severe periungual warts that affected six fingers; shown here (left) is an example of the extent of the lesions. After 3 months of combination therapy with liquid nitrogen, 40% urea gel, and imiquimod under occlusion, the warts began to resolve and complete clearance was achieved at 5 months on this regimen (right).

## Photodamage in a 46-Year-Old Woman

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this medication for 1 month—as well as the response of the other patients in the study—demonstrated that, in addition to its ability to correct epidermal dysplasia, imiquimod therapy appears to yield the added benefit of improvement in the early signs of photoaging. ■

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## Man With a Large Plantar Wart

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recurred during the intervening 4 years; examination confirmed the absence of a lesion. Presumably, the immune response modifier property of imiquimod enhanced the skin's response to applications of liquid nitrogen, permitting successful treatment of a previously recalcitrant and painful lesion. ■

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